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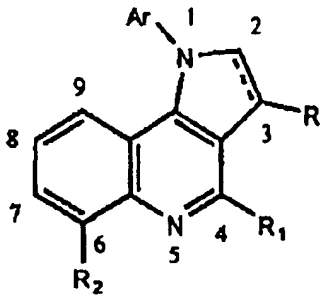

(1)

(57) Abstract

The present invention relates to 3-alkylpyrrolo[3,2-*c*]quinoline derivatives represented by formula (1), their pharmaceutically acceptable salts, process for preparation thereof, and pharmaceutical composition thereof for treating gastric ulcer. 3-Alkylpyrrolo[3,2-*c*]quinoline derivatives of the present invention and their salts which inhibit gastric acid secretion of mammal, can be used effectively as a treatment for gastric ulcer.

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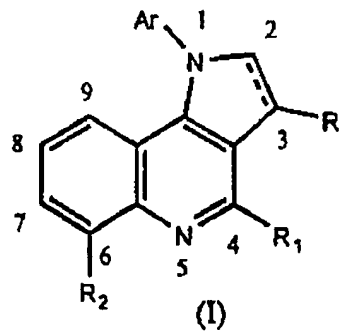
3-ALKYLPYRROLO[3,2-*c*]QUINOLINE DERIVATIVES

BACKGROUND OF THE INVENTION

The present invention relates to 3-alkylpyrrolo[3,2-*c*]quinoline derivatives represented by the formula 1, their pharmaceutically acceptable salts, process for preparation thereof, and pharmaceutical composition thereof for treating gastric ulcer.

More particularly, the present invention relates to 3-alkylpyrrolo[3,2-*c*]quinoline derivatives which inhibit gastric acid secretion of mammal; their salts; and process for preparation thereof. The pharmaceutical composition comprising quinoline derivatives of the present invention as an active ingredient is effective for inhibiting gastric acid secretion and treating gastric ulcer.

FORMULA 1



(I)

Wherein,

R is an alkyl group of C_{1-4}, may be substituted with hydroxy group, alkoxycarbonyl group of C_{1-4}, alkylcarbonyl group of C_{1-4}, arylcarbonyl group, aldehyde, alkoxy group of C_{1-4}, amino group, aminoalcohol, carboxy group, or halogen;

R_1 is hydrogen, alkyl of C_{1-6}, phenyl group, hydroxymethyl group, halogen, alkylthio group of C_{1-6}, alkoxy group of C_{1-6}, or amino group of C_{1-6} substituted or unsubstituted with hydroxy group;

R_2 is hydrogen, alkyl group of C_{1-6}, alkoxy group of C_{1-6} substituted or unsubstituted with hydroxy group or fluorine, hydroxy group, hydroxymethyl group, or amino group of C_{1-6}; and

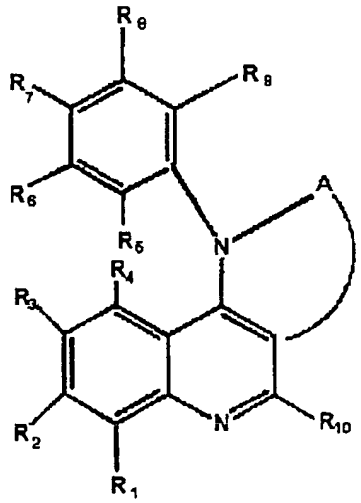
Ar is a phenyl or benzyl group substituted or unsubstituted with hydrogen, alkyl group of C_{1-6} substituted or unsubstituted with halogen, haloalkoxy group of C_{1-6} substituted or unsubstituted with halogen, alkylthio group of C_{1-6}, halogen, cyano group, amino group, nitro group, hydroxy group, etc.

So far, benzimidazole derivatives containing pyridine, as represented by the Omeprazole, have been commonly used as inhibitors of gastric acid secretion. Benzimidazole derivatives containing pyridine have displayed a prominent remedial result, but have raised a problem in long term administration because of their

irreversible reaction mechanism. That is, there have been a sustained effect of medicine after stopping administration or a side effect of stomach wall thickening by administration, etc.

On the one hand, quinoline derivatives have been known as an inhibitor for gastric acid secretion of mammal, and there have been attempts to develop them as a reversible inhibitor for gastric acid secretion. [EP Appl. 87-307824.0; USP 5,362,743; PCT/KR 94-29274; EP Appl. 89-301801.0; EP Appl. 89-301805.1; EP Appl. 89-301802.8; EP Appl. 88-306583.1; PCT/KR 97-00074; KR Pat. Appl. 96-38314; KR Pat. Appl. 97-30692; KR Pat. Appl. 97-30693; *J. Med. Chem.*, 1992, 35, 3413; and *J. Med. Chem.*, 1995, 38, 2742].

For example, EP Appl. 88-306583.1 describes pyrrolo[3,2-c]quinoline derivatives of the following structure.



Wherein,

A is -CH=CH-, $-(CH_2)_2-$ or $-(CH_2)_3-$;

R_1 to R_4 are hydrogen, alkyl group of C_{1-4}, alkoxy group of C_{1-6}, phenyl group, alkylthio group of C_{1-6}, alkanoyl group of C_{1-4}, amino group, alkylamino group of C_{1-6}, dialkylamino group of C_{1-6}, halogen, trifluoromethyl group or nitro group, respectively;

R_5 to R_9 are hydrogen, alkyl group of C_{1-6}, alkoxy group of C_{1-6}, alkylthio group of C_{1-6}, halogen, cyano group, amino group, hydroxy group, carbamoyl group, carbonyl group, alkanoyl group of C_{1-6}, trifluoromethyl group or nitro group, respectively; and

R_{10} is hydrogen, alkyl group of C_{1-6}, halogen, hydroxy group, $-CH_2OH$, alkylthio group of C_{1-6}, $NH(CH_2)_nOH$ (wherein n is 0 to 4) or $-NR_{11}R_{12}$.

The literature mentioned above described that compounds of the above formula and their salts acted as an inhibitor for gastric acid secretion by inhibiting gastric H^+/K^+-ATPase, and are useful for treating ulcers in mammal, particularly in human.

Also, in J. Med. Chem., 1992, 35, 1845-1852, it was described 1-arylpyrrolo[3,2-*c*]quinoline derivatives as a reversible inhibitor for gastric acid secretion, particularly on the effect of substituent R_{10}.

And KR Pat. Appl. 97-38512 describes the use of haloalkyl groups as R_1.

Despite of a good deal of effect, however, there has been no report about the introduction of substituent into 3-position since it is difficult to synthesize such compounds.

We, the inventors of the present invention, have investigated to develop a novel inhibitors for gastric acid secretion, and synthesized novel 3-alkylpyrrolo[3,2-*c*]quinoline derivatives and their salts by introducing various substituents into 3-position, which display an excellent inhibition of gastric acid secretion and stability. The synthesis was based on the application of a new synthetic method developed recently using palladium catalyst (*Tetrahedron Letter*, **1998**, *39*, 627 and *Heterocycles*, **1996**, *43*, 1641).

SUMMARY OF THE INVENTION

It is the object of the present invention to provide 3-alkylpyrrolo[3,2-*c*]quinoline derivatives represented by the formula 1 and their pharmaceutically acceptable salts.

It is another objective of the present invention to provide process for preparing 3-alkylpyrrolo[3,2-

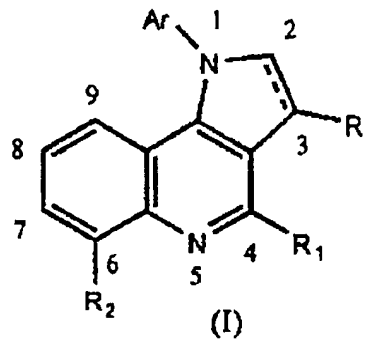
c]quinoline derivatives represented by the formula 1.

It is still another objective of the present invention to provide pharmaceutical composition for treating gastric ulcer, which comprises 3-alkylpyrrolo[3,2-*c*]quinoline derivatives represented by the formula 1 and their pharmaceutically acceptable salts as an active ingredient.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides 3-alkylpyrrolo[3,2-*c*]quinoline derivatives of formula 1, and their pharmaceutically acceptable salts:

FORMULA 1



(I)

wherein,

R is an alkyl group of C_{1-4}, may be substituted with hydroxy group, alkoxycarbonyl group of C_{1-4}, alkylcarbonyl group of C_{1-4}, arylcarbonyl group, aldehyde, alkoxy group of C_{1-4}, amino group,

aminoalcohol, carboxy group, or halogen;

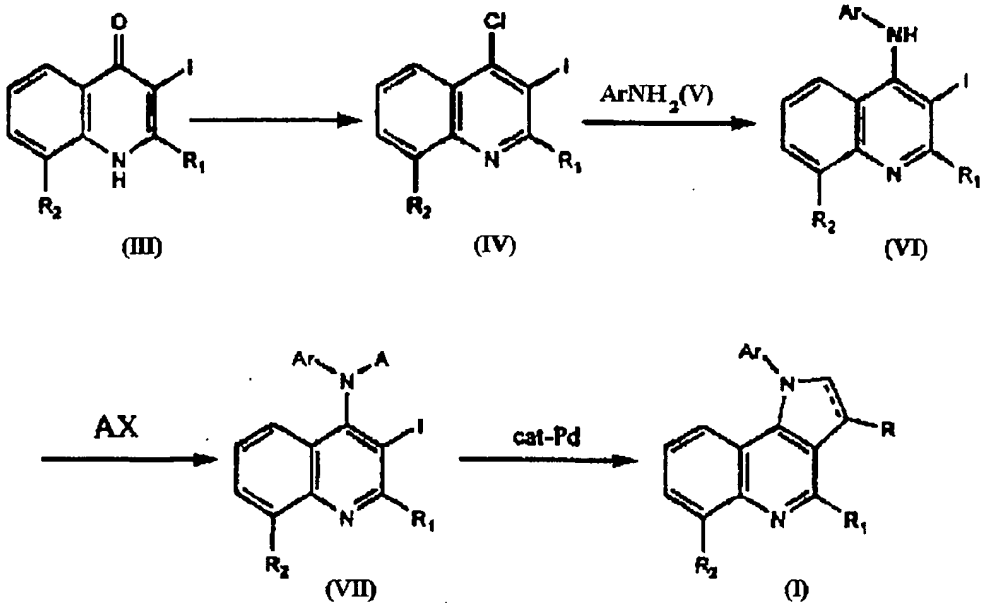
R_1 is hydrogen, alkyl of C_{1-6} phenyl group, hydroxymethyl group, halogen, alkylthio group of C_{1-6}, alkoxy group of C_{1-6}, or amino group of C_{1-6} substituted or unsubstituted with hydroxy group;

R_2 is hydrogen, alkyl group of C_{1-6}, alkoxy group of C_{1-6} substituted or unsubstituted with hydroxy group or fluorine, hydroxy group, hydroxymethyl group, or amino group of C_{1-6}; and

Ar is a phenyl or benzyl group substituted or unsubstituted with hydrogen, alkyl group of C_{1-6} substituted or unsubstituted with halogen, haloalkoxy group of C_{1-6} substituted or unsubstituted with halogen, alkylthio group of C_{1-6}, halogen, cyano group, amino group, nitro group, hydroxy group, etc.

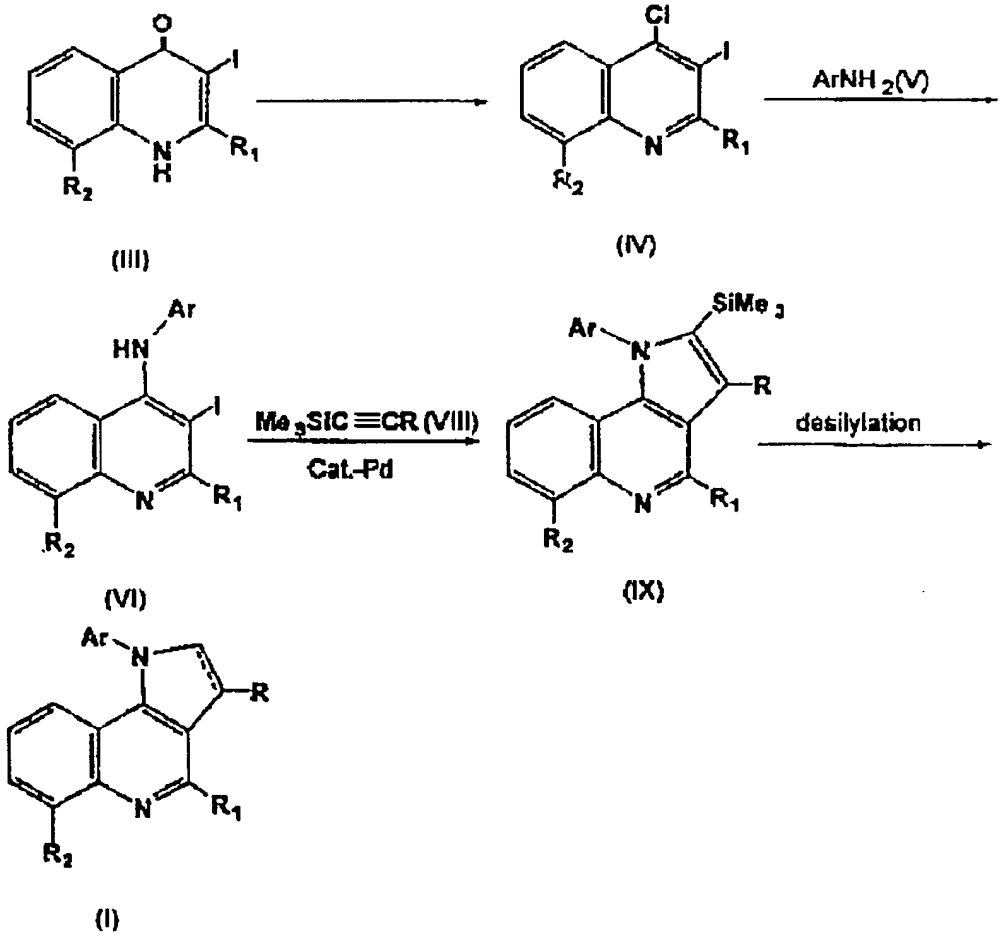
In addition, the present invention provides process for preparation of 3-alkylpyrrolo[3,2-*c*]quinoline derivatives. The compounds of the present invention can be prepared by two methods, process I represented by the following reaction scheme 1, and process II represented by the following reaction scheme 2.

REACTION SCHEME 1



(III) (IV) (VI) (VII) (I)

REACTION SCHEME 2



(III) (IV) (VI) (IX) (I)

The process for preparation according to the present invention, by the foregoing reaction scheme 1, comprises the steps of:

1) chlorinating a compound of formula (III) to give the quinoline substituted with chlorine, of formula (IV) (step 1);

2) reacting the quinoline substituted with chlorine, of formula (IV), with the aryl amine of formula (V) to give the quinoline of formula (VI) (step 2);

3) reacting the quinoline of formula (VI) with an allyl halide (AX) in the presence of a base to give the compound of formula (VII) (step 3); and

4) cyclizing the compound of formula (VII) with palladium catalyst to give the compound of formula 1 (step 4).

Also, the process for preparation according to the present invention, by the foregoing reaction scheme 2, comprises the steps of:

1) chlorinating a compound of formula (III) to give the quinoline substituted with chlorine, of formula (IV) (step 1);

2) reacting the quinoline substituted with chlorine, of formula (IV), with the aryl amine of formula (V) to give the quinoline of formula (VI) (step

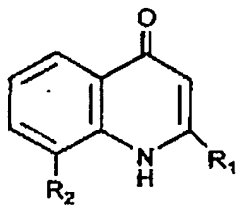
2);

3) reacting the quinoline of formula (VI) with the alkynes substituted with alkylsilane, of formula (VIII), to give the compound of formula (IX) (step 3); and

4) removing silyl group in the compound of formula (IX) to give the compound of formula 1 (step 4).

The compound of formula (III) used as a starting material in the process of the present invention, was obtained from the compound of the following formula (II) by the known method [*Synthesis*, **1977**, 865] by introducing iodine into 3-position of quinolone.

FORMULA 2



(II)

Wherein, R_1 and R_2 are defined as above.

The starting materials used in the present invention were synthesized according to a known method [Heterocyclic compounds, *Quinolines*, Vol. 32, PART 1].

The process of each step according to the present

invention will be described below in more detail.

At first, in the process I represented by the reaction scheme 1:

1) In the said reaction scheme 1, the compound of formula (III) is chlorinated with phosphoryl chloride ($POCl_3$), thionyl chloride ($SOCl_2$), phosphorus pentachloride (PCl_5), etc. to give the compound of formula (IV). In this reaction 1-10 equivalent of chlorinating reagent can be used, the reaction solvent may be selected from the group consisting of 1,2-dichloroethane, methylene chloride, etc. or the reaction can be performed without solvent.

2) The compound of formula (IV) and aryl amine (V) are reacted in 1,4-dioxane or in the absence of solvent, at 100-150 °C for 1-2 hours to give the compound of formula (VI). Here, the number of equivalents of aryl amine is preferably 1-10.

3) The compound of formula (VI) is reacted with various allyl halides in the presence of a base at room temperature for 2-3 hours to give the compound of formula (VII). Here, a solvent may be selected from the group consisting of tetrahydrofuran, methylene chloride, chloroform, diethyl ether, etc.

4) 3-Alkylpyrrolo[3,2-*c*]quinoline of formula 1 is obtained from the compound of formula (VII) by a cyclization reaction using palladium catalyst, a new heterocycle synthetic method [*Heterocycles*, **1996**, *43*, 1641]. In this reaction, 1-10 mol% of palladium catalyst, 1-5 equivalents of a base, and an organic or inorganic chloride salt are used, and the reactants are reacted in various solvents at 80-150 °C for 3-4 hours to give cyclized quinoline derivatives. It is preferable to use palladium acetate [$(CH_3COO)_2Pd$], potassium acetate (CH_3COOK), tetrabutylammonium chloride [$(n\text{-}Bu)_4NCl$] in tetrahydrofuran (THF).

Also, in the process II represented by the reaction scheme 2:

1) In the said reaction scheme 2, the compound of formula (III) is chlorinated with phosphoryl chloride ($POCl_3$), thionyl chloride ($SOCl_2$), phosphorus pentachloride (PCl_5), etc. to give the compound of formula (IV). In this reaction 1-10 equivalents of chlorinating reagent can be used, the reaction solvent may be selected from the group consisting of 1,2-dichloroethane, methylene chloride, etc. or the reaction can be performed without solvent.

2) The compound of formula (IV) and aryl amine (V)

are reacted in 1,4-dioxane or in the absence of solvent, at 100-150 °C for 1-2 hours to give the compound of formula (VI). Here, the number of equivalents of aryl amine is preferably 1-10.

3) The compound of formula (VI) and various alkynes of formula (VIII) substituted with alkylsilane, are reacted in various solvents by using a new heterocycle synthetic method [*Tetrahedron Letters*, **1998**, *39*, 627] to give a compound of formula (IX). At this time, 1-10 mol% of palladium catalyst, 1-5 equivalents of a base, and an organic or inorganic chloride are used, and the reactants are reacted by using various solvents at 80-150 °C for 4-8 hours to give a cyclized compound of formula (IX). The compound of formula (IX) is obtained easily by using preferably, palladium acetate, potassium acetate, lithium chloride (LiCl) in dimethylformamide (DMF).

4) Silyl group in the compound of formula (IX) is removed in the presence of acid catalyst in various solvents, to give the compound of formula 1.

3-Alkyl-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline, the compound of formula 1 of which 2- and 3-positioned carbon are saturated with hydrogen, is prepared by

selective hydrogenation reaction of 3-alkylpyrrolo[3,2-*c*]quinoline prepared according to the above processes I and II, with catalyst such as platinum oxide (PtO_2), sodium borohydride ($NaBH_4$), sodium cyanoborohydride ($NaBH_3CN$), etc. [*Reaction in Orgainc Chemistry*, **1984**, M. Hudlicky, Ellis Horwood Ltd., pp 55-57].

On the one hand, R_1 in the compound of formula 1 can be transformed into various functional groups by the known method [Heterocyclic Compound, Quinolines, Vol 32, Part I, II]. That is, in case of R_1 being CH_3, nitrogen at 5-position is oxidized with hydrogen peroxide to give 5-oxide, and the rearrangement in the presence of acetic anhydride and the hydrolysis transform the functional group into CH_2OH [*J. Am. Chem. Soc.* **1954**, 76, 1286]. In addition, in case of R_2 being hydrogen, chlorine is introduced into 4-position by reacting 5-oxide with phosphoryl chloride, sulfonyl halide, thionyl chloride, etc., and the compound in which chlorine is introduced into 4-position is reacted with various nucleophiles to give compounds wherein substituted amino, alkylthio or alkoxy is introduced into R_2 of the said formula 1 [*Chem. Abstr.*, **1951**, *45*, 8525; *Chem. Abstr.*, **1957**, *51*, 8742; *Chem. Abstr.*, **1958**, *52*, 14605].

Pharmaceutically acceptable salts of 3-alkylpyrrolo[3,2-*c*]quinoline derivatives prepared according to the above, can be prepared by using suitable organic or inorganic acids according to the general method. At this time, acids can be selected from the group consisting of hydrochloric acid, sulfuric acid, phosphoric acid, citric acid, maleic acid, formic acid, etc.

3-Alkylpyrrolo[3,2-*c*]quinoline derivatives of the present invention and their pharmaceutically acceptable salts inhibit reversibly gastric acid secretion, therefore pharmaceutical composition comprising them as an active ingredient is useful for inhibiting gastric acid secretion and treating gastric or duodenal ulcer.

Pharmaceutical composition for treatment of gastric ulcer, comprising 3-alkylpyrrolo[3,2-*c*]quinoline derivatives of the present invention and their salts as an active ingredient, can be prepared for oral or non-oral administration by mixing with generally-used nontoxic and pharmaceutically acceptable carrier and diluent in addition to the compound of the formula 1.

Pharmaceutical composition of the present invention can be prepared in type of oral administrable forms such as pill, troche, water-soluble or

oil-soluble suspension, powder, granule, emulsion, hard or soft capsule, syrup, or elixirs. For preparation of pill or capsule, binding agent such as lactose, sucrose, sorbitol, mannitol, starch, amylopectin, cellulose or gelatin; diluent such as dicalcium phosphate; dissolute such as corn starch or sweet potato starch; and lubricant such as magnesium stearate, calcium stearate, sodium stearyl fumarate or polyethylene glycol, etc. can be included. In case of preparation of capsule, liquid carrier like fatty oil can be included in addition to the above mentioned substances.

Also, pharmaceutical composition comprising the compound of the formula 1 as an active ingredient, can be prepared for injection, and such a preparation is administered by the method of hypodermic injection, intravenous injection, intramuscular injection or intrathoracic injection. To prepare such a preparation, the compound of the formula 1 and a stabilizer or damping agent in the water is mixed to make in the form of an aqueous solution or a suspension, and ampule or vial for unit dosage is prepared by using them.

3-Alkylpyrrolo[3,2-*c*]quinoline derivatives of the present invention and their pharmaceutically acceptable salts show a prominent inhibition on gastric acid

secretion, and can solve a problem in long term administration because of their reversible action mechanism in inhibiting gastric acid secretion, and therefore those can be used effectively as a new treatment for gastric ulcer.

Practically and presently preferred embodiments of the present invention are illustrative as shown in the following examples.

However, it will be appreciated that those skilled in the art, on consideration of this disclosure, may make modification and improvements within the spirit and scope of the present invention.

In the following examples, the process I was applied to examples 1-22, and the process II was applied to example 23 to prepare the compound of example 1. The compounds of examples 1-31 can be easily prepared by the process II described in the example 23.

<Example 1> Preparation of 6-methoxy-3-methyl-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline

(Step 1) Preparation of 3-iodo-4-(2-methylphenylamino)-8-methoxyquinoline

4-Chloro-3-iodo-8-methoxyquinoline (41.47 g, 0.13 mol) and 2-methylaniline (41 g, 0.4 mol) were refluxed

at 125 °C for 4 hours. The reaction mixture was dissolved in methylene chloride (600 ml) and washed with sodium bicarbonate aqueous solution, the organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to give the desired compound (42 g, 83%).

^{1}H NMR($CDCl_3$) δ 2.45(s, 3H), 4.07(s, 3H), 6.08(brs, 1H), 6.51(m, 1H), 6.96-7.30(m, 6H), 9.07(s, 1H).

m/e; 390(M^+).

m.p.; 155-156 °C.

(Step 2) Preparation of 6-methoxy-3-methyl-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline

To 3-iodo-4-(2-methylphenylamino)-8-methoxyquinoline (2.8 g, 7.1 mmol) in anhydrous tetrahydrofuran (20 ml) was added 60%-sodium hydride (NaH, 1 g), and the reaction mixture was stirred at room temperature for 1 hour. Allyl iodide (CH_2CHCH_2I, 2.8 g, 16 mmol) was added, and the mixture was stirred for 5 hours. To the intermediate obtained by adding saline to the reaction mixture and separating the organic layer were added tetrabutylammonium chloride [(n-Bu)$_4$NCl, 2.37 g, 6 mmol], sodium formate (0.84 g, 12 mmol), potassium acetate (1.34 g, 12 mmol) and

palladium acetate (80 mg) and the mixture in tetrahydrofuran (20 ml) was refluxed at 120 °C for 2 hours. The reaction mixture was concentrated and extracted with ethyl acetate, and the organic layer was separated. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to give the desired compound (1.4 g, 77%), and the compound was crystallized with a small amount of diethyl ether.

^{1}H NMR($CDCl_3$) δ 1.91(s, 3H), 2.52(s, 3H), 4.08(s, 3H), 6.66-7.49(m, 8H), 9.21(s, 1H).

m/e; 302(M^+).

m.p.; 131-133 °C .

<Example 2> Preparation of 3-ethyl-6-methoxy-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline

To 3-iodo-4-(2-methylphenylamino)-8-methoxyquinoline (1.17 g, 3.0 mmol) prepared by the process of the step 1 of example 1 in anhydrous tetrahydrofuran (20 ml) was added 60%-sodium hydride (NaH, 0.75 g) and the reaction mixture was stirred at room temperature for 1 hour. To this solution crotyl bromide ($CH_3CHCHCH_2Br$, 1.02 g, 7.5 mmol) was added, and the mixture was stirred for 5 hours. To the intermediate obtained by adding saline to the reaction

mixture and separating the organic layer were added tetrabutylammonium chloride (0.72 g, 3 mmol), sodium formate (0.42 g, 6 mmol), potassium acetate (0.61 g, 6 mmol) and palladium acetate (40 mg) and the mixture in tetrahydrofuran (15 ml) was refluxed at 120 °C for 2 hours. The reaction mixture was concentrated and extracted with ethyl acetate, and the organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to give the desired compound (0.4 g, 43%).

^{1}H NMR($CDCl_3$) δ 1.43(t, 3H), 1.92(s, 3H), 3.00(q, 2H), 6.67-7.49(m, 8H), 9.24(s, 1H).

m/e ; 316(M^+).

<Example 3> Preparation of 3-isopropyl-6-methoxy-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline

To 3-iodo-4-(2-methylphenylamino)-8-methoxyquinoline (0.78 g, 2 mmol) prepared by the process of the step 1 of example 1 dissolved in anhydrous tetrahydrofuran (20 ml) was added 60%-sodium hydride (NaH, 0.24 g), and the reaction mixture was stirred at room temperature for 1 hour. To this solution 4-bromo-2-methyl-1-butene (0.59 g, 4 mmol) was added, and the mixture was stirred for 5 hours. To the intermediate obtained by adding saline to the reaction

mixture and separating the organic layer were added tetrabutylammonium chloride (0.22 g, 1 mmol), sodium formate (0.14 g, 2 mmol), potassium acetate (0.2 g, 2 mmol) and palladium acetate (20 mg), and the mixture in tetrahydrofuran (15 ml) was refluxed at 120 °C for 2 hours. The reaction mixture was concentrated and extracted with ethyl acetate, and the organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to give the desired compound (0.18 g, 55%).

^{1}H NMR($CDCl_3$) δ 1.45(d, *J*=6.9Hz, 6H), 1.89(s, 3H), 3.43(m, 1H), 4.07(s, 3H), 6.67-7.47(m, 8H), 9.29(s, 1H).

m/e; 330(M^+).

<Example 4> Preparation of 1-(4-fluoro-2-methylphenyl)-6-methoxy-3-methyl-1*H*-pyrrolo[3,2-*c*]quinoline

(Step 1) Preparation of 4-(4-fluoro-2-methylphenylamino)-3-iodo-8-methoxyquinoline

4-Chloro-3-iodo-8-methoxyquinoline (3.83 g, 12 mmol) and 4-fluoro-2-methylaniline (2.3 g, 18 mmol) were refluxed at 125 °C for 4 hours. The mixture was dissolved in methylene chloride (70 ml) and washed with sodium bicarbonate aqueous solution, the organic layer

was separated, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to give the desired compound (4.67 g, 95%).

^{1}H NMR($CDCl_3$) δ 2.39(s, 3H), 4.05(s, 3H), 5.97(brs, 1H), 6.47-7.20(m, 6H), 9.02(s, 1H).

m/e; 408(M^+).

m.p.; 150-151 °C.

(Step 2) Preparation of 1-(4-fluoro-2-methylphenyl)-6-methoxy-3-methyl-1*H*-pyrrolo[3,2-*c*]quinoline

4-(4-Fluoro-2-methylphenylamino)-3-iodo-8-methoxyquinoline (0.5 g, 1.2 mmol) in anhydrous tetrahydrofuran (20 ml) was added 60%-sodium hydride (NaH, 0.2 g), and the reaction mixture was stirred at room temperature for 1 hour. To this solution was added allyl iodide (CH_2CHCH_2I, 0.55 g, 4 mmol), and the mixture was stirred for 5 hours. To the intermediate obtained by adding saline to the reaction mixture and separating the organic layer were added tetrabutylammonium chloride (0.22 g, 1 mmol), sodium formate (0.14 g, 2 mmol), potassium acetate (0.2 g, 2 mmol) and palladium acetate (40 mg) and the mixture in tetrahydrofuran (15 ml) was refluxed at 120 °C for 2 hours. The reaction mixture was concentrated and extracted with ethyl acetate, and the organic layer was

separated, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to give the desired compound (0.18 g, 64%), and the compound was crystallized with a small amount of diethyl ether.

^{1}H NMR($CDCl_3$) δ 1.88(s, 3H), 2.49(s, 3H), 4.06(s, 3H), 6.64-7.37(m, 7H), 9.18(s, 1H).

m/e; 320(M^+).

m.p.; 156-158 °C.

<Example 5> Preparation of 3-ethyl-1-(4-fluoro-2-methylphenyl)-6-methoxy-1*H*-pyrrolo[3,2-*c*]quinoline

To 4-(4-fluoro-2-methylphenylamino)-3-iodo-8-methoxyquinoline (0.55 g, 1.36 mmol), prepared by the process of the step 1 of example 4 in anhydrous tetrahydrofuran (20 ml) was added 60%-sodium hydride (NaH, 0.2 g), and the reaction mixture was stirred at room temperature for 1 hour. To this solution an excess of crotyl bromide ($CH_3CHCHCH_2Br$) was added dropwise, and the mixture was stirred for 5 hours. To the intermediate (0.5 g, 80%) obtained by adding saline to the reaction mixture and separating the organic layer were added tetrabutylammonium chloride (0.25 g, 1.08 mmol), sodium formate (0.15 g, 2.16 mmol), potassium acetate (0.25 g, 2.16 mmol) and palladium acetate (20 mg), and the mixture in tetrahydrofuran (10 ml) was

refluxed at 120 °C for 2 hours. The reaction mixture was concentrated and extracted with ethyl acetate, and the organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to give the desired compound (0.2 g, 56%), and the compound was crystallized with a small amount of diethyl ether.

^{1}H NMR($CDCl_3$) δ 1.42(t, 3H), 1.89(s, 3H), 2.97(q, 2H), 4.08(s, 3H), 6.63-7.41(m, 7H), 9.22(s, 1H).

m/e; 334(M^+).

m.p.; 174-175 °C.

<Example 6> Preparation of 1-(4-hydroxy-2-methylphenyl)-6-methoxy-3-methyl-1*H*-pyrrolo[3,2-*c*]quinoline

(Step 1) Preparation of 4-(4-benzyloxy-2-methylphenylamino)-3-iodo-8-methoxyquinoline

4-Chloro-3-iodo-8-methoxyquinoline (5.1 g, 16 mmol) and 4-benzyloxy-2-methylaniline (6.8 g, 32 mmol) were refluxed at 125 °C for 4 hours. The reaction mixture was dissolved in methylene chloride (100 ml) and washed with sodium bicarbonate aqueous solution, the organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*,

and the residue was purified by silica gel column chromatography to give the desired compound (6.5 g, 82%).

^{1}H NMR($CDCl_3$) δ 2.38(s, 3H), 4.08(s, 3H), 5.06(s, 2H), 6.10(brs, 1H), 6.61-7.48(m, 11H), 9.02(s, 1H)

m/e; 496(M^+).

m.p.; 162-163 °C.

(Step 2) Preparation of 3-methyl-6-methoxy-1-(4-benzyloxy-2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline

To 4-(4-benzyloxy-2-methylphenylamino)-3-iodo-8-methoxyquinoline (1 g, 2 mmol) in anhydrous tetrahydrofuran (20ml) was added 60%-sodium hydride (NaH, 0.5 g), and the reaction mixture was stirred at room temperature for 1 hour. To this solution was added allyl iodide (0.7 g, 4 mmol), and the mixture was stirred for 5 hours. To the intermediate obtained by adding saline to the reaction mixture and separating the organic layer were added tetrabutylammonium chloride (0.47 g, 2 mmol), sodium formate (0.27 g, 4 mmol), potassium acetate (0.4 g, 4 mmol) and palladium acetate (23 mg), and the mixture in tetrahydrofuran (20 ml) was refluxed at 120 °C for 2 hours. The reaction mixture was concentrated and extracted with ethyl acetate, and the organic layer was separated, dried over anhydrous magnesium sulfate, filtered and

concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to give the desired compound (0.56 g, 68%), and the compound was crystallized with a small amount of diethyl ether.

^{1}H NMR($CDCl_3$) δ 1.86(s, 3H), 2.50(s, 3H), 4.08(s, 3H), 5.16(s, 2H), 6.72-7.52(m, 12H), 9.18(s, 1H).

m/e; 408(M^+).

m.p.; 163-164 °C.

(Step 3) Preparation of 1-(4-hydroxy-2-methylphenyl)-6-methoxy-3-methyl-1*H*-pyrrolo[3,2-*c*]quinoline

3-Methyl-6-methoxy-1-(4-benzyloxy-2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline (0.45 g, 1.1 mmol) in methanol (20 ml) was stirred in the presence of 5%-palladium catalyst and hydrogen (H_2, 40 psi) at room temperature for 2 hours. The reaction mixture was filtered and concentrated to give the desired compound (50 mg, 15%).

^{1}H NMR($CDCl_3$) δ 1.08(s, 3H), 2.49(s, 3H), 4.02(s, 3H), 6.76-7.18(m, 7H), 9.16(s, 1H).

m/e; 318(M^+).

m.p.; 270 °C.

<Example 7> Preparation of 1-(4-hydroxy-2-methylphenyl)-3-ethyl-6-methoxy-1*H*-pyrrolo[3,2-

c]quinoline

(Step 1) Preparation of 1-(4-benzyloxy-2-methylphenyl)-3-ethyl-6-methoxy-1*H*-pyrrolo[3,2-*c*]quinoline

To 4-(4-benzyloxy-2-methylphenylamino)-3-iodo-8-methoxyquinoline (1 g, 2 mmol) in anhydrous tetrahydrofuran (20 ml) was added 60%-sodium hydride (NaH, 0.5 g), and the mixture was stirred at room temperature for 1 hour. To this solution crotyl bromide ($CH_3CHCHCH_2Br$, 0.63 g, 4 mmol) was added, and the mixture was stirred for 5 hours. To the intermediate obtained by adding saline to the reaction mixture and separating the organic layer were added tetrabutylammonium chloride (0.47 g, 2 mmol), sodium formate (0.27 g, 4 mmol), potassium acetate (0.4 g, 4 mmol) and palladium acetate (23 mg), and the mixture in tetrahydrofuran (20 ml) was refluxed at 120 °C for 2 hours. The reaction mixture was concentrated and extracted with ethyl acetate, and the organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to give the desired compound (0.25 g, 30%), and the compound was crystallized with a small amount of diethyl ether.

^{1}H NMR($CDCl_3$) δ 1.42(t, 3H), 1.87(s, 3H), 2.97(q, 2H), 4.08(s, 3H), 5.17(s, 2H), 6.75-7.50(m, 12H), 9.18(s, 1H).

m/e; 422(M^+).

m.p.; 55-57 °C.

(Step 2) Preparation of 1-(4-hydroxy-2-methylphenyl)-3-ethyl-6-methoxy-1*H*-pyrrolo[3,2-*c*]quinoline

1-(4-Benzyloxy-2-methylphenyl)-3-ethyl-6-methoxy-1H-pyrrolo[3,2-*c*]quinoline (0.25 g, 0.59 mmol) prepared in the step 1 of example 7 in methanol (10 ml) was stirred in the presence of 5%-palladium catalyst and hydrogen (H_2, 40 psi) at room temperature for 2 hours. The reaction mixture was filtered and concentrated to give the desired compound (0.12 g, 62%).

^{1}H NMR(DMSO-d_6) δ 1.45(t, 3H), 1.82(s, 3H), 2.98(s, 2H), 4.07(s, 3H), 6.80-7.25(m, 7H), 9.15(s, 1H).

m/e; 332(M^+).

m.p.; 247-250 °C.

<Example 8> Preparation of 1-(4-hydroxy-2-methylphenyl)-3-isopropyl-6-methoxy-1*H*-pyrrolo[3,2-*c*]quinoline

1-(4-Benzyloxy-2-methylphenyl)-3-isopropyl-6-methoxy-1*H*-pyrrolo[3,2-*c*]quinoline (448 mg, 1.03 mmol) prepared by the process of the step 1 of example 7 in methanol (10 ml) was stirred in the presence of 5%-palladium catalyst and hydrogen (H_2, 40 psi) at room

temperature for 2 hours. The reaction mixture was filtered and concentrated to give the desired compound (240 mg, 69%).

^{1}H NMR(DMSO-d_6) δ 1.45(d, 6H), 1.78(s, 3H), 3.41(m, 1H), 4.08(s, 3H), 6.76-7.23(m, 7H), 9.23(s, 1H).

m/e; 346(M^+).

m.p.; 264-266 °C.

<Example 9> Preparation of 6-methoxy-3-methyl-1-(1-phenylethyl)-1*H*-pyrrolo[3,2-*c*]quinoline

(Step 1) Preparation of 3-iodo-8-methoxy-4-(1-phenylethylamino)quinoline

4-Chloro-3-iodo-8-methoxyquinoline (2 g, 6.2 mmol) and 1-phenyl-1-ethylamine (2 g, 16 mmol) were refluxed at 125 °C for 4 hours. The reaction mixture was dissolved in methylene chloride (50 ml) and washed with sodium bicarbonate aqueous solution, the organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to give the desired compound (1.6 g, 63%).

^{1}H NMR($CDCl_3$) δ 1.64(d, 3H), 4.04(s, 3H), 4.70(brd, 1H), 5.10(m, 1H), 6.97-7.53(m, 8H), 8.87(s, 1H).

m/e; 404(M^+).

m.p.; 166-167 °C.

(Step 2) Preparation of 6-methoxy-3-methyl-1-(1-phenylethyl)-1*H*-pyrrolo[3,2-*c*]quinoline

To 3-iodo-8-methoxy-4-(1-phenylethylamino) quinoline (0.6 g, 4.4 mmol) in anhydrous tetrahydrofuran (20 ml) was added 60%-sodium hydride (NaH, 0.2 g), and the mixture was stirred at room temperature for 1 hour. To this solution was added an excess of allyl iodide, and the mixture was stirred for 5 hours. To the intermediate obtained by adding saline to the reaction mixture and separating the organic layer were added tetrabutylammonium chloride (0.39 g, 1.7 mmol), sodium formate (0.23 g, 3.4 mmol), potassium acetate (0.34 g, 3.4 mmol) and palladium acetate (20 mg), and the mixture in tetrahydrofuran (10 ml) was refluxed at 120 °C for 2 hours. The reaction mixture was concentrated and extracted with ethyl acetate, and the organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to give the desired compound (0.4 g, 70%), and the compound was crystallized with a small amount of diethyl ether.

^{1}H NMR($CDCl_3$) δ 1.96(s, 3H), 2.45(s, 3H), 4.05(s, 3H), 6.29(q, 1H), 6.92-7.71(m, 9H), 9.13(s, 1H).

m/e; 316(M^+).

m.p.; 142-144 °C.

<Example 10> Preparation of 3-ethyl-6-methoxy-1-(1-phenylethyl)-1*H*-pyrrolo[3,2-*c*]quinoline

The reaction with 4-chloro-3-iodo-8-ethoxyquinoline in place of 4-chloro-3-iodo-8-methoxyquinoline as a starting material, was performed by the same method in the example 9 to give the desired compound.

^{1}H NMR($CDCl_3$) δ 1.42(t, 3H), 2.04(d, 3H), 2.96(q, 2H), 4.07(s, 3H), 6.34(q, 1H), 6.97-7.76(m, 9H), 9.22(s, 1H).

m/e; 330(M^+).

m.p.; 89-90 °C.

<Example 11> Preparation of 6-methoxy-3,4-dimethyl-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline

(Step 1) Preparation of 3-iodo-8-methoxy-2-methyl-4-(2-methylphenylamino)quinoline

4-Chloro-3-iodo-8-methoxy-2-methylquinoline (33 g, 0.1 mol) and 2-methylaniline (30 g, 0.27 mol) were refluxed at 125 °C for 4 hours. The reaction mixture was dissolved in methylene chloride (400 ml) and washed with sodium bicarbonate aqueous solution, the organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the residue was purified by silica gel column

chromatography to give the desired compound (30 g, 75%).

^{1}H NMR($CDCl_3$) δ 2.45(s, 3H), 3.04(s, 3H), 4.06(s, 3H), 6.13(brs, 1H), 6.41(m, 1H), 6.93-7.28(m, 6H).

m/e; 404(M^+).

(Step 2) Preparation of 6-methoxy-3,4-dimethyl-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline

To 3-iodo-8-methoxy-2-methyl-4-(2-methylphenylamino)quinoline (2.8 g, 7.1 mmol) in anhydrous tetrahydrofuran (30 ml) was added 60%-sodium hydride (NaH, 1 g), and the mixture was stirred at room temperature for 1 hour. To this solution was added an excess of allyl iodide, and the mixture was stirred for 5 hours. To the intermediate obtained by adding saline to the reaction mixture and separating the organic layer were added tetrabutylammonium chloride (2.37 g, 6 mmol), sodium formate (0.84 g, 12 mmol), potassium acetate (1.34 g, 12 mmol) and palladium acetate (80 mg), and the mixture in tetrahydrofuran (20 ml) were refluxed at 120 °C for 2 hours. The reaction mixture was concentrated and extracted with ethyl acetate, and the organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to give the desired compound (1.4 g,

77%), and the compound was crystallized with a small amount of diethyl ether.

^{1}H NMR($CDCl_3$) δ 1.92(s, 3H), 2.61(s, 3H), 3.10(s, 3H), 4.05(s, 3H), 6.60-7.50(m, 8H).

m/e; 316(M^+).

<Example 12> Preparation of 3-ethyl-6-methoxy-4-methyl-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline

The reaction with crotyl bromide in place of allyl halide, was performed by the same process of the example 11 to give the desired compound.

^{1}H NMR($CDCl_3$) δ 1.40(t, *J*=7.3Hz, 3H), 1.91(s, 3H), 3.09(q, *J*=7.3Hz, 2H), 3.10(s, 3H), 4.05(s, 3H), 6.60-7.52(m, 8H).

m/e; 330(M^+).

<Example 13> Preparation of 1-(4-fluoro-2-methylphenyl)-6-methoxy-3,4-dimethyl-1*H*-pyrrolo[3,2-*c*]quinoline

(Step 1) Preparation of 4-(4-fluoro-2-methylphenylamino)-3-iodo-8-methoxy-2-methylquinoline

4-Chloro-3-iodo-8-methoxy-2-methylquinoline (7 g, 20.9 mmol) and 4-fluoro-2-methylaniline (5 g, 40 mmol) were refluxed at 125 °C for 4 hours. The mixture was dissolved in methylene chloride (100 ml) and washed

with sodium bicarbonate aqueous solution, the organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to give the desired compound (6 g, 68%).

^{1}H NMR($CDCl_3$) δ 2.42(s, 3H), 3.04(s, 3H), 4.05(s, 3H), 6.04(brs, 1H), 6.37-7.17(m, 6H).

m/e; 422(M^+).

m.p.; 180-181 °C.

(Step 2) Preparation of 1-(4-fluoro-2-methylphenyl)-6-methoxy-3,4-dimethyl-1*H*-pyrrolo[3,2-*c*]quinoline

To 4-(4-fluoro-2-methylphenylamino)-3-iodo-8-methoxy-2-methylquinoline (0.89 g, 1.2 mmol) in anhydrous tetrahydrofuran (30 ml) was added 60%-sodium hydride (NaH, 0.3 g), and the mixture was stirred at room temperature for 1 hour. To this solution was added an excess of allyl iodide, and the mixture was stirred for 5 hours. To the intermediate obtained by adding saline to the reaction mixture and separating the organic layer were added tetrabutylammonium chloride (0.48 g, 2.1 mmol), sodium formate (0.28 g, 4.2 mmol), potassium acetate (0.41 g, 4.2 mmol) and palladium acetate (23 mg), and the mixture in tetrahydrofuran (20 ml) was refluxed at 120 °C for 2 hours. The reaction mixture was concentrated and extracted with ethyl

acetate, and the organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to give the desired compound (0.33 g, 47%), and the compound was crystallized with a small amount of diethyl ether.

^{1}H NMR($CDCl_3$) δ 1.86(s, 3H), 2.57(s, 3H), 3.06(s, 3H), 4.01(s, 3H), 6.55-7.33(m, 7H).

m/e; 334(M^+).

m.p.; 199-200 °C.

<Example 14> Preparation of 3-ethyl-4-methyl-6-methoxy-1-(4-fluoro-2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline

To 4-(4-fluoro-2-methylphenylamino)-3-iodo-8-methoxy-2-methylquinoline (0.89 g, 1.2 mmol) prepared by the process of the step 1 of example 13 in anhydrous tetrahydrofuran (30 ml) was added 60%-sodium hydride (NaH, 0.5 g), and the reaction mixture was stirred at room temperature for 1 hour. To this solution was added crotyl bromide ($CH_3CHCHCH_2Br$, 0.67 g, 5.0 mmol), and the mixture was stirred for 5 hours. To the intermediate obtained by adding saline to the reaction mixture and separating the organic layer were added tetrabutylammonium chloride (0.48 g, 2.1 mmol), sodium formate (0.28 g, 4.2 mmol), potassium acetate (0.41 g, 4.2 mmol) and palladium acetate (23 mg), and the

mixture in tetrahydrofuran (20 ml) was refluxed at 120 °C for 2 hours. The reaction mixture was concentrated and extracted with ethyl acetate, and the organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to give the desired compound (0.37 g, 51%), and the compound was crystallized with a small amount of diethyl ether.

^{1}H NMR($CDCl_3$) δ 1.39(t, 3H), 1.89(s, 3H), 3.09(q, 2H), 3.10(s, 3H), 4.04(s, 3H), 6.61-7.39(m, 7H).

m/e ; 348(M^+)

m.p. ; 162.5-136.5 °C.

<Example 15> Preparation of 6-hydroxy-3-methyl-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline

To 6-methoxy-3-methyl-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline (0.86 g, 2.84 mmol) prepared by the process of step 1 and 2 of example 11 with 3-iodo-8-methoxy-4-(2-methylphenylamino)quinoline in place of 3-iodo-8-methoxy-2-methyl-4-(2-methylphenylamino) quinoline in methylene chloride (20 ml) was added dropwise slowly boron tribromide (BBr_3, 1 g, 3.9 mmol), and the reaction mixture was stirred at room temperature for 2 hours. The mixture was washed with dilute aqueous soda solution, the organic layer was

separated, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to give the desired compound (0.57 g, 70%).

^{1}H NMR($CDCl_3$) δ 1.89(s, 3H), 2.49(s, 3H), 6.49(dd, 1H), 6.89-7.50(m, 7H), 9.00(s, 1H).

m/e ; 228(M^+).

m.p.; 137-139 °C.

<Example 16> Preparation of 6-(2-hydroxyethoxy)-3-methyl-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline

6-Hydroxy-3-methyl-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline (0.29 g, 1 mmol) prepared by the process of step 1 and 2 of example 11 with 3-iodo-8-hydroxy-4-(2-methylphenyl)quinoline in place of 3-iodo-8-methoxy-2-methyl-4-(2-methylphenylamino) quinoline, ethylene carbonate (1,3-dioxolan-2-one, 3 g) and potassium carbonate (K_2CO_3, 0.3 g) were refluxed at 130 °C for 3 hours. The reaction mixture was dissolved in methylene chloride (20 ml), washed with distilled water, the organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to give the desired compound (0.3 g, 90%).

^{1}H NMR($CDCl_3$) δ 1.93(s, 3H), 2.54(s, 3H), 4.04(t, *J*=4.3Hz,2H), 4.32(t, *J*=4.3Hz, 2H), 6.72-7.52(m, 8H), 9.16(s, 1H).

m/e; 332(M^+).

<Example 17> Preparation of 6-trifluoromethoxy-3-methyl-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline

(Step 1) Preparation of ethyl 4-oxo-8-trifluoromethoxy-1,4-dihydro-3-quinolinecarboxylate

The mixture of 2-trifluoromethoxyaniline (17.7 g, 0.1 mol) and diethyl ethoxy methylene malonate(17.7 g, 0.1 mol) was refluxed at 90 °C for 30 minutes. The intermediate obtained by concentrating the mixture *in vacuo* to remove the ethanol produced during reaction, was dissolved in diphenyl ether (200 ml), and the mixture was refluxed at 260 °C for 2 hours. The mixture was allowed to cool to room temperature, petroleum ether (200 ml) was added, and the mixture was stirred for 30 minutes. The solid produced was filtered to give the desired compound (23.1 g, 77%).

^{1}H NMR(DMSO-d_6) δ 1.30(t, 3H), 4.25(q, 2H), 7.50(t, 1H), 7.82(d, 1H), 8.18(d, 1H), 8.42(d, 1H), 12.38(d, 1H).

m/e; 301(M^+)

m.p.; 228-230 °C.

(Step 2) Preparation of 8-trifluoromethoxy-1,4-dihydro-4-quinolinone

140 ml of 10%-soda aqueous solution was added to ethyl 4-oxo-8-trifluoromethoxy-1,4-dihydro-3-quinolinecarboxylate (30.1 g, 0.1 mol), and the reaction mixture was refluxed for 3 hours. The mixture was allowed to cool to room temperature, neutralized (pH= 2) with dilute hydrochloric acid to give a white solid, and the solid was separated and dried. Diphenyl ether (250 ml) was added to the solid, and the solution was refluxed at 260 °C for 3 hours. The mixture was allowed to cool to room temperature, poured into petroleum ether (250 ml) and stirred for 30 minutes. The solid produced was filtered to give the desired compound (22 g, 96%).

^{1}H NMR(DMSO-d_6) δ 6.15(d, 1H), 7.40-8.10(m, 4H), 11.85(brs, 1H).

m/e; 229(M^+).

m.p.; 145-146 °C.

(Step 3) Preparation of 3-iodo-8-trifluoromethoxy-1,4-dihydro-4-quinolinone

8-Trifluoromethoxy-1,4-dihydro-4-quinolinone (22.9 g, 0.1 mol) was dissolved in 10%-soda solution (200 ml), iodine (36.5 g) was dissolved in 20%-potassium

iodide aqueous solution, and the latter solution was added dropwise slowly to the former. The mixture was stirred at room temperature for 3 hours. The solid produced by adding the excess of acetic acid and distilled water (300 ml) to the mixture, was filtered to give the desired compound (27.6 g, 79%)

^{1}H NMR(DMSO-d_6) δ 7.50(t, 1H), 7.83(d, 1H), 8.18(d, 1H), 8.43(d, 1H), 12.40(br, 1H).

m/e; 355(M^+)

m.p.; 278-279 °C.

(Step 4) Preparation of 4-chloro-3-iodo-8-trifluoromethoxyquinoline

The mixture of 3-iodo-8-trifluoromethoxy-1,4-dihydro-4-quinolinone (33 g) and phosphorus oxychloride (80 ml) was refluxed at 110 °C for 1 hour, the mixture was poured slowly into ice water, neutralized with dilute soda solution to give a solid, and the solid produced was filtered to give the desired compound (33.5 g, 95%).

^{1}H NMR($CDCl_3$) δ 7.60-7.75(m, 2H), 8.25(dd, 1H), 9.21(s, 1H).

m/e; 373(M^+)

m.p.; 95-96 °C.

(Step 5) Preparation of 3-iodo-4-(2-methylphenylamino)-

8-trifluoromethoxyquinoline

The mixture of 4-chloro-3-iodo-8-trifluoromethoxyquinoline (10 g, 26.8 mmol) and 2-methylaniline (10 g) was refluxed at 125 °C for 4 hours. The mixture was dissolved in methylene chloride (100 ml), washed with sodium bicarbonate aqueous solution, the organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to give the desired compound (9 g, 76%).

^{1}H NMR($CDCl_3$) δ 2.42(s, 3H), 6.18(s, 1H), 6.59(m, 1H), 7.00-7.56(m, 6H), 9.12(s, 1H).

m/e; 444(M^+).

m.p.; 104-106 °C.

(Step 6) Preparation of 6-trifluoromethoxy-3-methyl-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline

To 3-iodo-4-(2-methylphenylamino)-8-trifluoromethoxyquinoline (1.14 g, 2.5 mmol) in anhydrous tetrahydrofuran (20 ml) was added 60%-sodium hydride (NaH, 0.3 g), and the mixture was stirred at room temperature for 1 hour. To this solution was added ally iodide (2.8 g, 16 mmol), and the mixture was stirred for 5 hours. To the intermediate obtained by adding saline to the mixture and separating the organic

layer were added tetrabutylammonium chloride (0.45 g, 2 mmol), sodium formate (0.28 g, 4 mmol), potassium acetate (0.45 g, 4 mmol) and palladium acetate (30 mg), and the mixture in tetrahydrofuran (10 ml) was refluxed at 120 °C for 2 hours. The mixture was concentrated and extracted with ethyl acetate, and the organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to give the desired compound (0.25 g, 28%), and the compound was crystallized with a small amount of diethyl ether.

^{1}H NMR($CDCl_3$) δ 1.92(s, 3H), 2.52(s, 3H), 6.95-7.50(m, 8H), 9.28(s, 1H).

m/e; 356(M^+), 341(15.6), 271(11.8), 257(11.8), 255(19.8), 69(79.2).

m.p.; 103-105 °C.

<Example 18> Preparation of 3-ethyl-6-trifluoromethoxy-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline

To 3-iodo-4-(2-methylphenylamino)-8-trifluoromethoxyquinoline (1.14 g, 2.5 mmol) prepared by the process of step 1-5 of example 17 in anhydrous tetrahydrofuran (20 ml) was added 60%-sodium hydride (NaH, 0.3 g), and the mixture was stirred at room temperature for 1 hour. To this solution was added crotyl bromide ($CH_3CHCHCH_2Br$, 2.8 g, 16 mmol), and the

mixture was stirred for 5 hours. To the intermediate obtained by adding saline to the mixture and separating the organic layer were added tetrabutylammonium chloride (0.45 g, 2 mmol), sodium formate (0.28 g, 4 mmol), potassium acetate (0.45 g, 4 mmol) and palladium acetate (30 mg), and the mixture in tetrahydrofuran (10 ml) was refluxed at 120 °C for 2 hours. The mixture was concentrated and extracted with ethyl acetate, and the organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to give the desired compound (0.33 g, 35%).

^{1}H NMR($CDCl_3$) δ 1.42(t, 3H), 1.95(s, 3H), 2.98(q, 2H), 6.95-7.55(m, 8H), 9.31(s, 1H).

m/e ; 370(M^+), 355(100), 69(60).

<Example 19> Preparation of 3-isopropyl-6-trifluoromethoxy-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline

To 3-iodo-4-(2-methylphenylamino)-8-trifluoromethoxyquinoline (1.14 g, 2.5 mmol) prepared by the process of step 1-5 of example 17 in anhydrous tetrahydrofuran (20 ml) was added 60%-sodium hydride (NaH, 0.3 g), and the mixture was stirred at room temperature for 1 hour. To this solution was added 4-

bromo-2-methyl-1-butene (2.8 g, 16 mmol), and the mixture was stirred for 5 hours. To the intermediate obtained by adding saline to the reaction mixture and separating the organic layer were added tetrabutylammonium chloride (0.45 g, 2 mmol), sodium formate (0.28 g, 4 mmol), potassium acetate (0.45 g, 4 mmol) and palladium acetate (30 mg), and the mixture in tetrahydrofuran (10 ml) was refluxed at 120 °C for 2 hours. The mixture was concentrated and extracted with ethyl acetate, and the organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to give the desired compound (0.23 g, 24%), and the compound was crystallized with a small amount of diethyl ether.

^{1}H NMR($CDCl_3$) δ 1.45(d, 6H), 1.92(s, 3H), 3.41(m, 1H), 6.94(s, 1H), 7.00-7.55(m, 7H), 9.37(s, 1H).

m/e; 384(M^+), 370(24.2), 369(100), 69(31.5).

m.p.; 111-112 °C.

<Example 20> Preparation of 1-(4-fluoro-2-methylphenyl)-6-trifluoromethoxy-3-methyl-1*H*-pyrrolo[3,2-*c*]quinoline

(Step 1) Preparation of 4-(4-fluoro-2-methylphenylamino)-3-iodo-8-trifluoromethoxyquinoline

4-Chloro-3-iodo-8-trifluoromethoxyquinoline (4.25 g, 11.3 mmol) and 4-fluoro-2-methylaniline (4.25 g) were refluxed at 125 °C for 36 hours. The mixture was dissolved in methylene chloride (100 ml) and washed with sodium bicarbonate, the organic layer was separated , dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to give the desired compound (4.5 g, 86%).

^{1}H NMR($CDCl_3$) δ 2.40(s, 3H), 6.10(brs, 1H), 6.55-7.55(m, 6H), 9.10(s, 1H).

m/e; 462(M^+).

m.p.; 116-117 °C.

(Step 2) Preparation of 1-(4-fluoro-2-methylphenyl)-6-trifluoromethoxy-3-methyl-1*H*-pyrrolo[3,2-*c*]quinoline

To 4-(4-fluoro-2-methylphenylamino)-3-iodo-8-trifluoromethoxyquinoline (1.14 g, 2.5 mmol) in anhydrous tetrahydrofuran (20 ml) was added 60%-sodium hydride (NaH, 0.3 g), and the mixture was stirred at room temperature for 1 hour. To this solution was added allyl iodide (2.8 g, 16 mmol), and the mixture was stirred for 5 hours. To the intermediate obtained by adding saline to the mixture and separating the organic layer were added tetrabutylammonium chloride (0.45 g, 2 mmol), sodium formate (0.28 g, 4 mmol), potassium

acetate (0.45 g, 4 mmol) and palladium acetate (30 mg), and the mixture in tetrahydrofuran (10 ml) was refluxed at 120 °C for 2 hours. The mixture was concentrated and extracted with ethyl acetate, and the organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to give the desired compound (0.25 g, 27%), and the compound was crystallized with a small amount of diethyl ether.

^{1}H NMR($CDCl_3$) δ 1.90(s, 3H), 2.54(s, 3H), 6.92(s, 1H), 7.00-7.47(m, 6H), 9.26(s, 1H).

m/e; 374(M^+, 100), 359(7.4), 69(72.4).

m.p.; 129-131 °C.

<Example 21> Preparation of 3-ethyl-1-(4-fluoro-2-methylphenyl)-6-trifluoromethoxy-1*H*-pyrrolo[3,2-*c*]quinoline

To 4-(4-fluoro-2-methylphenylamino)-3-iodo-8-trifluoromethoxyquinoline (1.14 g, 2.5 mmol) prepared by the process of step 1 of example 20 in anhydrous tetrahydrofuran (20 ml) was added 60%-sodium hydride (NaH, 0.3 g), and the mixture was stirred at room temperature for 1 hour. To this solution was added crotyl bromide ($CH_3CHCHCH_2Br$, 2.8 g, 16 mmol), and the mixture was stirred for 5 hours. To the intermediate obtained by adding saline to the mixture and separating

the organic layer were added tetrabutylammonium chloride (0.45 g, 2 mmol), sodium formate (0.28 g, 4 mmol), potassium acetate (0.45 g, 4 mmol) and palladium acetate (30 mg), and the mixture in tetrahydrofuran (10 ml) was refluxed at 120 °C for 2 hours. The mixture was concentrated and extracted with ethyl acetate, and the organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to give the desired compound (0.24 g, 25%), and the compound was crystallized with a small amount of diethyl ether.

^{1}H NMR($CDCl_3$) δ 1.42(t, 3H), 1.91(s, 3H), 2.97(q, 2H), 7.02-7.47(m, 6H), 9.30(s, 1H).

m/e; 389(M^++1, 54.7), 388(M^+), 373(100), 358(5.7), 303(14.5), 287(10), 273(11.4), 69(34.2).

m.p.; 155-156 °C.

<Example 22> Preparation of 6-(2,2,2-trifluoroethoxy)3-methyl-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline

(Step 1) Preparation of ethyl 4-oxo-8-(2,2,2-trifluoroethoxy)-1,4-dihydro-3-quinolinecarboxylate

The mixture of 2-(2,2,2-trifluoroethoxy)aniline (19.1 g, 0.1 mol) and diethyl ethoxy methylene malonate (17.7 g, 0.1 mol) was refluxed at 90 °C for 30 minutes.

The intermediate obtained by concentrating the mixture *in vacuo* to remove the ethnaol produced during reaction, was dissolved in diphenyl ether (200 ml), and the mixture was refluxed at 260 °C for 2 hours. The mixture was allowed to cool to room temperature, petroleum ether (200 ml) was added, and the mixture was stirred for 30 minutes. The solid produced was filtered to give the desired compound (25.2 g, 80%).

^{1}H NMR(DMSO-d_6) δ 1.30(t, 3H), 4.24(q, 2H), 5.05(q, 2H), 7.35-7.85(m, 3H), 8.42(br, 1H), 11.80(brd, 1H).

m/e; 315(M^+).

m.p.; 236-238 °C.

(Step 2) Preparation of 8-(2,2,2-trifluoroethoxy)-1,4-dihydro-4-quinolinone

10%-soda aqueous solution (140 ml) was added to ethyl 4-oxo-8-(2,2,2-trifluoroethoxy)-1,4-dihydro-3-quinolinecarboxylate (31.5 g, 0.1 mol) and the reaction mixture was refluxed for 3 hours. The mixture was allowed to cool to room temperature, neutralized to pH 2 with dilute hydrochloric acid to give a white solid, and the solid was separated and dried. Diphenyl ether (250 ml) was added to the solid, and the solution was refluxed at 260 °C for 3 hours. The mixture was allowed to cool to room temperature, poured into petroleum ether (250 ml) and stirred for 30 minutes. The solid

produced was filtered to give the desired compound (23 g, 95%).

^{1}H NMR(DMSO-d_6) δ 4.98(q, 2H), 6.07(d, 1H), 7.21-7.85(m, 4H), 11.25 (brs, 1H).

m/e; 243(M^+).

m.p.; 173-175 °C.

(Step 3) Preparation of 3-iodo-8-(2,2,2-trifluoroethoxy)-1,4-dihydro-4-quinolinone

8-(2,2,2-Trifluoroethoxy)-1,4-dihydro-4-quinolinone (24.3 g, 0.1 mol) was dissolved in 10%-soda solution (200 ml), iodine (36.5 g) was dissolved in 20%-potassium iodide aqueous solution, and the latter solution was added dropwise slowly to the former. The reaction mixture was stirred at room temperature for 3 hours. The solid produced by adding the excess of acetic acid and distilled water (300 ml) to the mixture, was filtered to give the desired compound (30.6 g, 83%)

^{1}H NMR(DMSO-d_6) δ 5.00(q, 2H), 7.29-8.30(m, 4H), 11.65(br, 1H).

m/e; 369(M^+).

m.p.; 187-189 °C.

(Step 4) Preparation of 4-chloro-3-iodo-8-(2,2,2-trifluoroethoxy)quinoline

The mixture of 3-iodo-8-(2,2,2-trifluoroethoxy)-1,4-dihydro-4-quinolinone (9.2 g, 24.9 mmol) and phosphorus oxychloride (20 ml) was refluxed at 110 °C. After the reaction for 1 hour, the mixture was poured slowly into ice water and neutralized with dilute soda solution, and the organic layer was extracted with ethyl acetate and separated. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrate *in vacuo*, and the residue was purified by silica gel column chromatography to give the desired compound (8.0 g, 83%).

^{1}H NMR($CDCl_3$) δ 4.47(q, 2H), 7.30(d, 1H), 7.56(t, 1H), 7.99(q, 1H), 9.13(s, 1H).

m/e; 387(M^+).

m.p.; 135-136 °C.

(Step 5) Preparation of 3-iodo-4-(2-methylphenylamino)-8-(2,2,2-trifluoroethoxy)quinoline

The mixture of 4-chloro-3-iodo-8-(2,2,2-trifluoroethoxy)quinoline (6.9 g, 17.8 mmol) and 2-methylaniline (8.0 g) was refluxed at 125 °C for 4 hours. The mixture was dissolved in methylene chloride (100 ml) and washed with sodium bicarbonate aqueous solution, and the organic layer was separated. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the

residue was purified by silica gel column chromatography to give the desired compound (7.0 g, 85%).

^{1}H NMR($CDCl_3$) δ 2.42(s, 3H), 4.72(q, 2H), 6.10(brs, 1H), 6.50-7.30(m, 7H), 9.07(s, 1H).

m/e; 458(M^+).

m.p.; 115-117 °C.

(Step 6) Preparation of 6-(2,2,2-trifluoroethoxy)-3-methyl-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline

To 3-iodo-4-(2-methylphenylamino)-8-(2,2,2-trifluoroethoxy)quinoline (1.15 g, 2.5 mmol) in anhydrous tetrahydrofuran (20 ml) was added 60%-sodium hydride (NaH, 0.3 g), and the reaction mixture was stirred at room temperature for 1 hour. To this solution was added ally iodide (2.8 g, 16 mmol), and the mixture was stirred for 5 hours. To the intermediate obtained by adding saline to the mixture and separating the organic layer were added tetrabutylammonium chloride (0.45 g, 2 mmol), sodium formate (0.28 g, 4 mmol), potassium acetate (0.45 g, 4 mmol) and palladium acetate (30 mg), and the mixture in tetrahydrofuran (10 ml) was refluxed at 120 °C for 2 hours. The mixture was concentrated and extracted with ethyl acetate, and the organic layer was separated. The organic layer was dried over anhydrous magnesium

sulfate, filtered and concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to give the desired compound (0.5 g, 54%).

^{1}H NMR($CDCl_3$) δ 1.90(s, 3H), 2.52(s, 3H), 4.78(q, 2H), 6.80-7.50(m, 8H), 9.22(s, 1H).

m/e; 370(M^+).

The following examples 23-31 relates to the preparation of 3-alkylpyrrolo[3,2-*c*]quinoline derivatives according to the process II.

<Example 23> Preparation of 6-methoxy-3-methyl-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline

(Step 1) Preparation of 6-methoxy-3-methyl-1-(2-methyl)-2-trimethylsilyl-1*H*-pyrrolo[3,2-*c*]quinoline

3-Iodo-4-(2-methylphenylamino)-8-methoxyquinoline (2 g, 5.3 mmol), trimethylsilyl-1-propyne (1.8 g, 16 mmol), lithium chloride (0.22 g, 5.3 mmol), potassium acetate (1 g, 10.6 mmol) and palladium acetate (59 mg, 5 mmol%) in dimethylformamide (50 ml), were refluxed at 100 °C for 4 hours. The mixture was concentrated *in vacuo* and the organic layer was extracted with diethyl ether. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*,

the residue was purified by silica gel column chromatography to give the desired compound (1.51 g, 72%), and the compound was crystallized with a small amount of diethyl ether.

^{1}H NMR($CDCl_3$) δ 0.10(s, 9H), 1.85(s, 3H), 2.64(s, 3H), 4.08(s, 3H), 6.45-7.49(m, 7H), 9.20(s, 1H).

m/e; 376(M^+).

(Step 2) Preparation of 6-methoxy-3-methyd-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline

6-Methoxy-3-methyl-1-(2-methyl)-2-trimethylsilyl-1*H*-pyrrolo[3,2-*c*]quinoline (1.51 g, 4 mmol) in trifluoroacetic acid (TFA, 8 ml) was refluxed for 3 hours. The mixture was concentrated and the organic layer was separated by extraction with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, the residue was purified by silica gel column chromatography to give the desired compound (1.1 g, 92%), and the compound was crystallized with a small amount of diethyl ether.

The compounds of examples 24-31 were prepared by the same process of example 23, with 3-trimethylsilyl-2-propyn-1-ol in place of trimethylsilyl-1-propyne.

<Example 24> Preparation of 6-methoxy-3-hydroxymethyl-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline

Yield=82%.

^{1}H NMR($CDCl_3$) δ 1.91(s, 3H), 2.10(brs,1H), 4.08(s, 3H), 5.10 (s, 2H), 6.66-7.49(m, 8H), 9.21(s, 1H).

m/e; 318(M^+).

m.p.; 96-98 °C.

<Example 25> Preparation of 1-(4-fluoro-2-methylphenyl)-6-methoxy-3-hydroxymethyl-1*H*-pyrrolo[3,2-*c*]quinoline

Yield=80%.

^{1}H NMR($CDCl_3$) δ 1.88(s, 3H), 2.25(brs, 1H), 4.06(s, 3H), 5.10(s, 2H), 6.64-7.37(m, 7H), 9.18(s, 1H).

m/e; 336(M^+).

m.p.; 168-170 °C.

<Example 26> Preparation of 1-(4-methoxy-2-methylphenyl)-6-methoxy-3-hydroxymethyl-1*H*-pyrrolo[3,2-*c*]quinoline

Yield=78%.

^{1}H NMR($CDCl_3$) δ 1.80(s, 3H), 2.25(s, 1H), 4.02(s, 3H), 5.10(s,2H), 6.76-7.18(m, 7H), 9.16(s, 1H).

m/e; 334(M^+).

m.p.; 198-200 °C.

<Example 27> Preparation of 6-methoxy-3-(2-hydroxyethyl)-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline

Yield=75%.

^{1}H NMR($CDCl_3$) δ 1.91(s, 3H), 2.10(brs, 1H), 3.20(t, 2H), 4.00(t, 2H), 4.08 (s, 3H), 6.66-7.49(m, 8H), 9.21(s, 1H).

m/e; 332(M^+).

m.p.; 86-88 °C.

<Example 28> Preparation of 1-(4-fluoro-2-methylphenyl)-6-methoxy-3-(2-hydroxyethyl)-1*H*-pyrrolo[3,2-*c*]quinoline

Yield=79%.

^{1}H NMR($CDCl_3$) δ 1.88(s, 3H), 2.25(brs, 1H), 3.20(t,2H), 4.00(t,2H), 4.06(s, 3H), 6.64-7.37(m, 7H), 9.18(s, 1H).

m/e; 350(M^+).

m.p.; 150-152 °C.

<Example 29> Preparation of 1-(4-methoxy-2-methylphenyl)-6-methoxy-3-(2-hydroxyethyl)-1*H*-pyrrolo[3,2-*c*]quinoline

Yield=73%.

^{1}H NMR($CDCl_3$) δ 1.80(s, 3H), 2.25(s, 1H), 3.20(t,

2H), 4.00(t, 2H), 4.02(s, 3H), 6.76-7.18(m, 7H), 9.16(s, 1H).

m/e; 348(M^+).

m.p.; 170-172 °C.

<Example 30> Preparation of 1-(4-methoxy-2-methylphenyl)-6-methoxy-3-methyl-1*H*-pyrrolo[3,2-*c*]quinoline

Yield=74%.

^{1}H NMR($CDCl_3$) δ 1.88(s, 3H), 2.51(s, 3H), 3.92(s, 3H), 4.09(s, 3H), 6.73-7.31(m, 7H), 9.19(s, 1H).

m/e; 332(M^+).

m.p.; 192.5-193.5 °C.

<Example 31> Preparation of 1-(4-methoxy-2-methylphenyl)-6-methoxy-3-ethyl-1*H*-pyrrolo[3,2-*c*]quinoline

Yield=78%.

^{1}H NMR($CDCl_3$) δ 1.39(t, 3H), 1.84(s, 3H, J = 7.5 Hz), 2.95(q, 2H, J = 7.5 Hz), 3.88(s, 3H), 4.05(s, 3H), 6.70-7.30(m, 7H), 9.19(s, 1H).

m/e; 346(M^+).

m.p.; 138-140 °C.

3-Alkylpyrrolo[3,2-*c*]quinoline derivatives of the

present invention as well as the compounds of examples 1-31, can be prepared easily by the processes I and II.

The preparation examples of pharmaceutical composition comprising 3-alkylpyrrolo[3,2-*c*]quinoline derivatives of the present invention and their pharmaceutically acceptable salts as an active ingredient, are described below.

The following preparation examples are just representative examples of the present invention, and never limit the scope of the present invention.

<Preparation Example 1> Preparation of syrup comprising 3-alkylpyrrolo[3,2-*c*]quinoline derivatives as an active ingredient

Syrup comprising 2 % (wt/vol.) of 3-alkylpyrrolo[3,2-*c*]quinoline derivatives of the present invention and their pharmaceutically acceptable salts, was prepared by the following process.

Acid salt of 3-alkylpyrrolo[3,2-c]quinoline derivatives, sugar and saccharin were dissolved in 80 g of warm distilled water, the solution was allowed to cool, and then the solution consisting of glycerin, saccharin, sweetener, sorbic acid and distilled water was added to the above solution. Distilled water was

added to the solution until the volume of the solution was 100 ml. The acid part of 3-alkylpyrrolo[3,2-c]quinoline derivatives can be substituted with another acid.

The followings are the components of the syrup.

6-Methoxy-3-methyl-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline·HCl salt	2 g
Saccharin	0.8 g
Sugar	25.4 g
Glycerin	8.0 g
Sweetener	0.04 g
Ethanol	4.0 g
Sorbic acid	0.4 g
Distilled water	q.s.

<Preparation Example 2> Preparation of pill comprising 3-alkylpyrrolo[3,2-*c*]quinoline derivatives as an active ingredient

Pill comprising 15 mg of 3-alkylpyrrolo[3,2-*c*]quinoline derivatives and their pharmaceutically acceptable salts, was prepared by the following process.

250 g of 6-methoxy-3-methyl-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline·HCl salt was mixed with 175.9

g of lactose, 180 g of corn starch and 32 g of colloidal silicic acid. 10% Gelatin solution was added to the mixture, and the mixture was pulverized, filtered with No. 14 mesh sieve and dried. Hereto was added 160 g of potato starch, 50 g of talc and 5 g of magnesium stearate to obtain the mixture, and the mixture was prepared in type of pill. The followings are the components of the pill prepared by the above process.

6-Methoxy-3-methyl-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline·HCl salt	250 g
Lactose	175.9 g
Corn starch	180 g
Colloidal silicic acid	32 g
Potato starch	160 g
Talc	50 g
Magnesium stearate	5 g
10 % Gelatin solution	

<Preparation Example 3> Preparation of ampule comprising 3-alkylpyrrolo[3,2-*c*]quinoline derivatives as an active ingredient

Ampule comprising 10 mg of 3-alkylpyrrolo[3,2-*c*]quinoline derivatives and their pharmaceutically

acceptable salts, was prepared by the following process.

1 g of 6-methoxy-3-methyl-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline·HCl salt, 0.6 g of sodium chloride and 0.1 g of ascorbic acid were dissolved in distilled water, to prepare 100 ml of solution. This solution was put into the bottle, and pasteurized by heating at 20 °C for 30 minutes. The followings are the components of the ampule prepared by the above process.

6-Methoxy-3-methyl-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline·HCl salt	1 g
Sodium chloride	0.6 g
Ascorbic acid	0.1 g
Distilled water	q.s.

Dose of 3-alkylpyrrolo[3,2-*c*]quinoline derivatives represented by the formula 1 according to the present invention, can be varied in accordance with the age, weight, gender, type of administration, health of patient and severity of disease, however, dose per day is preferably 15-25 mg on the basis of adult male.

To confirm the prominent effect on inhibiting gastric acid secretion of 3-alkylpyrrolo[3,2-

c]quinoline derivatives represented by the formula 1 according to the present invention, *in vivo* assay of pharmacological activity was performed.

<Experiment 1> *In vivo* assay of pharmacological activity

In vitro enzyme assay of H^+/K^+-ATPase collected from a pig stomach was carried out, wherein the negative control was the activity of H^+/K^+-ATPase stimulated by Mg^{2+} and the positive control was the activity of H^+/K^+-ATPase stimulated by Mg^{2+} and K^+.

Sprague Dawley male rats (150-200 g, 6 weak-old) were fasted for 24 hours, and the compound of the present invention suspended in 0.5% CMC, was orally administered in 30, 100, 300 mg/kg dose. After 1 hour, 1 ml of 97% ethanol was orally administered, and the mouse was sacrificed an hour later with ether. Stomach was resected, 13 ml of 1% formalin was injected into stomach, and the stomach was put into 1% formalin solution and fixed for 1 hour. The stomach was incised along greater curvature and opened, and the length of gastric ulcer was measured and compared with that of the control to which only solvent was administered, to calculate % protection and to determine the 50% protection dose.

The result was shown in the following table 1.

TABLE 1

Example No. of compound	Inhibition rate of gastric ulcer relative to Omeprazole	*In vitro* enzymatic reaction
1	+++	+++
2	++	+
3	+	++
4	+++	++
5	+++	+++
7	+	+++
8	+	+++
15	+	+++

* Relative *in vivo* pharmaceutical efficacy to comparative compound; +++(strong), ++(similar), +(weak)
* Omeprazole; compound of EP No. 9105959.0

As a result, it was confirmed that 3-alkylpyrrolo[3,2-c]quinoline derivatives according to the present invention and their pharmaceutically acceptable salts inhibit more prominently the gastric acid secretion than Omeprazole.

<Experiment 2> Toxicity test

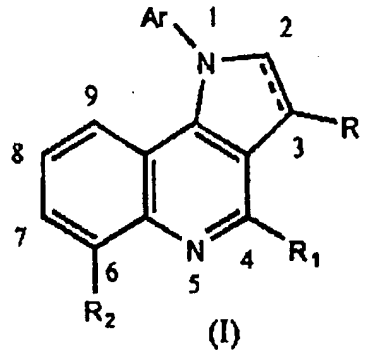
3000 mg/kg of the compound of example 5, which had been suspended in 5% CMC, was administered to 5 white

mice, the acute toxicity did not appear and any abnormality was not found for 2 weeks. 300 mg/kg/day of the compound of example 1 was administered to 5 Sprague Dawley male rats (150-200 g) for 3 weeks. The rats grew without any abnormality, and there was no abnormality in the rats sectioned after stopping administration.

What is claimed is :

1. 3-Alkylpyrrolo[3,2-*c*]quinoline derivatives represented by the formula 1, and their pharmaceutically acceptable salts:

FORMULA 1



(I)

wherein

R is an alkyl group of C_{1-4}, may be substituted with hydroxy group, alkoxycarbonyl group of C_{1-4}, alkylcarbonyl group of C_{1-4}, arylcarbonyl group, aldehyde, alkoxy group of C_{1-4}, amino group, aminoalcohol, carboxy group, or halogen;

R_1 is hydrogen, alkyl of C_{1-6}, phenyl group, hydroxymethyl group, halogen, alkylthio group of C_{1-6}, alkoxy group of C_{1-6}, or amino group of C_{1-6} substituted or unsubstituted with hydroxy group;

R_2 is hydrogen, alkyl group of C_{1-6}, alkoxy group of C_{1-6} substituted or unsubstituted with hydroxy group or fluorine, hydroxy group, hydroxymethyl group, or amino

group of C_{1-3}; and

Ar is a phenyl or benzyl group substituted or unsubstituted with hydrogen, alkyl group of C_{1-6} substituted or unsubstituted with halogen, haloalkoxy group of C_{1-3} substituted or unsubstituted with halogen, alkylthio group of C_{1-6}, halogen, cyano group, amino group, nitro group, hydroxy group, etc.

2. 3-Alkylpyrrolo[3,2-*c*]quinoline derivatives and their pharmaceutically acceptable salts according to claim 1, wherein

R is an alkyl group of C_{1-4}, and may be substituted with hydroxy group, alkoxycarbonyl group of C_{1-4}, alkylcarbonyl group of C_{1-4}, arylcarbonyl group or aldehyde;

R_1 is hydrogen or methyl group;

R_2 is hydrogen, alkoxy group of C_{1-3} substituted or unsubstituted with fluorine, hydroxy group, or 2-hydroxyethoxy group; and

Ar is a phenyl or benzyl group substituted or unsubstituted with hydrogen, alkyl group of C_{1-3} substituted or unsubstituted with halogen, or hydroxy group.

3. 3-Alkylpyrrolo[3,2-*c*]quinoline derivatives and their pharmaceutically acceptable salts according to

claim 1, wherein the compound of formula 1 is 6-methoxy-3-methyl-1-(2-methylphenyl)-1*H*-pyrrolo[3,2-*c*]quinoline.

4. 3-Alkylpyrrolo[3,2-*c*]quinoline derivatives and their pharmaceutically acceptable salts according to claim 1, wherein the compound of formula 1 is 1-(4-fluoro-2-methylphenyl)-6-methoxy-3-methyl-1*H*-pyrrolo[3,2-*c*]quinoline.

5. 3-Alkylpyrrolo[3,2-*c*]quinoline derivatives and their pharmaceutically acceptable salts according to claim 1, wherein the compound of formula 1 is 3-ethyl-1-(4-fluoro-2-methylphenyl)-6-methoxy-1*H*-pyrrolo[3,2-*c*]quinoline.

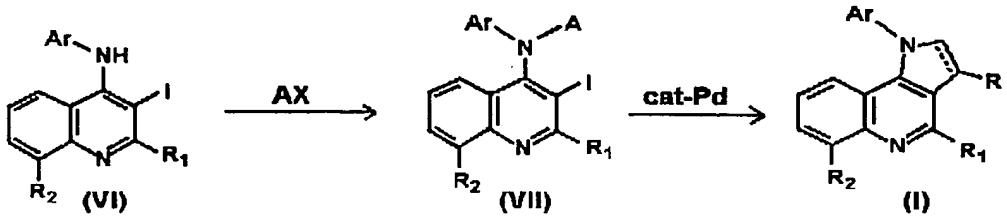
6. A process for preparing 3-alkylpyrrolo[3,2-*c*]quinoline derivatives, represented by reaction scheme 3, characterized by comprising the steps of:

1) reacting the compound of formula (VI) with allyl halide (AX) in the presence of a base to give N-allyl quinoline derivative of formula (VII); and

2) cyclizing the compound of formula (VII) using palladium catalyst (cat-Pd) to give the compound of

formula 1.

REACTION SCHEME 3



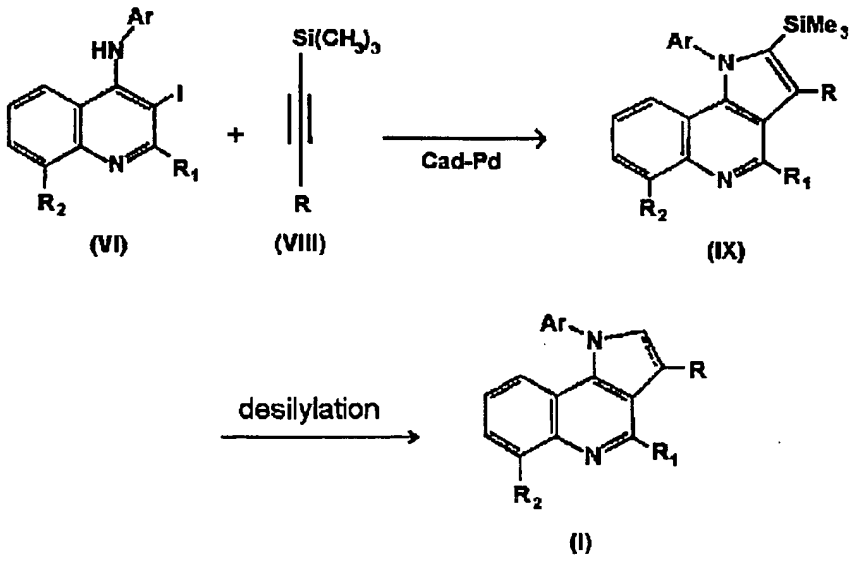
Wherein, R, R_1, R_2 and Ar are defined as above.

7. A process for preparing 3-alkylpyrrolo[3,2-c]quinoline derivatives, represented by reaction scheme 4, comprising the steps of:

1) cyclizing the quinoline compound of formula (VI) and silyl alkyne of formula (VIII) using palladium catalyst to give the compound of formula (IX); and

2) removing silyl group in the compound of formula (IX) to give the compound of formula 1.

REACTION SCHEME 4



Wherein, R, R_1, R_2 and Ar are defined as above.

8. A pharmaceutical composition for treating gastric ulcer, which comprises 3-alkylpyrrolo[3,2-c]quinoline derivatives represented by the formula 1 and their pharmaceutically acceptable salts as an active ingredient.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 99/00346

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: C 07 D 471/04; A 61 K 31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: C 07 D 471/00, 215/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT, Chem.Abstr.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Questel: DARC, CAS; EPO: WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 307 078 A1 (SMITHKLINE BECKMANN), 15 March 1989 (15.03.89), claims.	1-8
P,A	WO 99/09 029 A1 (KOREA RESEARCH INSTITUTE OF CHEMICAL TECHNOLOGY), 25 February 1999 (25.02.99), claims.	1-8
A	Chemical Abstract, Vol 112, No.7, 12 February 1990 (12.02.90), (Columbus, Ohio, USA), page 14, column 1, abstract No.48250q, T.BROWN et al.:"Reversible inhibitors of the gastric (H+/K+)-ATPase. 1. 1-Aryl-4-methylpyrrolo[3,2-c]quinolines as conformationally restrained analogs of 4-(arylamino)quinolines", J.Med.Chem.33(2), 527-33 (1990).	1,8

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
„A" document defining the general state of the art which is not considered to be of particular relevance
„E" earlier application or patent but published on or after the international filing date
„L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
„O" document referring to an oral disclosure, use, exhibition or other means
„P" document published prior to the international filing date but later than the priority date claimed
„T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
„X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
„Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
„&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
01 September 1999 (01.09.99)	10 September 1999 (10.09.99)

Name and mailing adress of the ISA/AT	Authorized officer
Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/200	Hammer Telephone No. 1/53424/374

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 99/00346

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chemical Abstracts, Vol.116, No.25, 12 June 1992 (12.06.92), (Columbus, Ohio, USA), page 779, column 2, abstract No.255506a, C.LEACH et al.:"Reversible inhibitors of the gastric (H+/K+)-ATPase. 2. 1-Arylpyrrolo[3,2-c]quinolines: effect of the 4-substituent", J.Med.Chem., 1845-52 (1992).	1,8

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR 99/00346

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		DE T2 3874056	07-01-1993
		DK A0 4144/88	22-07-1988
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		PT A 88033	30-06-1989
		PT B 88033	31-03-1995
		US A 5051508	24-09-1991
		ZA A 8805311	26-07-1989
WO A1 9909029	25-02-1999	keine - none - rien	